View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Lirias

Quick guide

Calcium-induced calcium release

H. Llewelyn Roderick, Michael J. Berridge and Martin D. Bootman

Why is calcium so important? Intracellular calcium controls a diverse array of cellular processes from fertilisation through gene transcription, muscle contraction to cell death. Changes in calcium levels can occur in microseconds or hours, they can be microscopic or propagate throughout cells and tissues.

How are calcium levels increased within cells? Increases in intracellular calcium arise through either calcium influx across the plasma membrane or release from intracellular calcium stores, which is usually either the endoplasmic reticulum (ER) or, in muscle, the sarcoplasmic reticulum (SR). Release of calcium from the ER/SR is activated by a variety of second messengers, such as inositol 1,4,5-trisphosphate (IP_3), cyclic ADP ribose (cADPr) or, significantly, by calcium itself.

What is calcium-induced calcium release? This is the process — commonly known by the acronym CICR — whereby calcium promotes its own release from intracellular calcium stores. The diffusion of calcium within cells is greatly retarded by buffers. CICR therefore provides a means for amplification of microscopic initiation events into propagating calcium signals. For calcium to control cellular activities it has to reach targets that may be distant from initiation sites. Without CICR, cells would have to rely on the slow dissipative diffusion of calcium.

What channels mediate CICR? IP_3 receptors and ryanodine receptors are the major calcium release channels that display CICR. These structurally related channels are widely expressed and mediate calcium release in muscle, neurons and non-excitable cells. IP_3 dictates the sensitivity of IP_3 receptors to calcium. Calcium can directly activate ryanodine receptors, although cADPr may also act as a sensitiser.

How does calcium modulate release channel activity? Calcium binding sites have been found in the primary sequences of both ryanodine receptors and IP_3 receptors. CICR therefore occurs via direct binding of calcium to channels. In addition to the direct binding, calcium exerts some effects through accessory proteins such as calmodulin. IP_3 receptors and ryanodine receptors exist as macromolecular complexes containing proteins such as kinases and phosphatases which serve to regulate the sensitivity of these channels to calcium.

Where does CICR occur in biology? During each heartbeat an influx of calcium through L-type voltage-operated channels provides the trigger to induce CICR from juxtaposed ryanodine receptors on the SR, resulting in cardiac muscle contraction. Examples of CICR in non-excitable cells include IP_3-induced calcium oscillations and waves following fertilisation of mammalian eggs, and the spread of calcium waves in pancreatic acinar cells that underlie zymogen granule exocytosis and fluid secretion.

Are there any other manifestations of CICR? Although IP_3 receptors and ryanodine receptors are believed to be the primary CICR channels, a few other forms of CICR have been reported. For example, a protein, polycystin 2, which is mutated in autosomal dominant polycystic kidney disease has been shown to operate as a CICR channel. The permeability transition pore of mitochondria can open in response to elevated matrix calcium levels. This results in the rapid release of calcium from mitochondria, which can affect neighbouring mitochondria leading to a propagating signal. The term CICR is most commonly used to imply the activation of release channels by the direct binding of calcium. Calcium can, however, also modulate the activity of enzymes that produce calcium-mobilising metabolites such as IP_3, arachidonic acid and nitric oxide.

Where can I find out more?

Bootman, M.D., Berridge, M.J. and Roderick, H.L. (2002). Calcium signalling: more messengers, more channels, more complexity. Curr. Biol. *12*, R563–R565.

Laboratory of Molecular Signalling, The Babraham Institute, Babraham, Cambridge, CB2 4AT, UK.

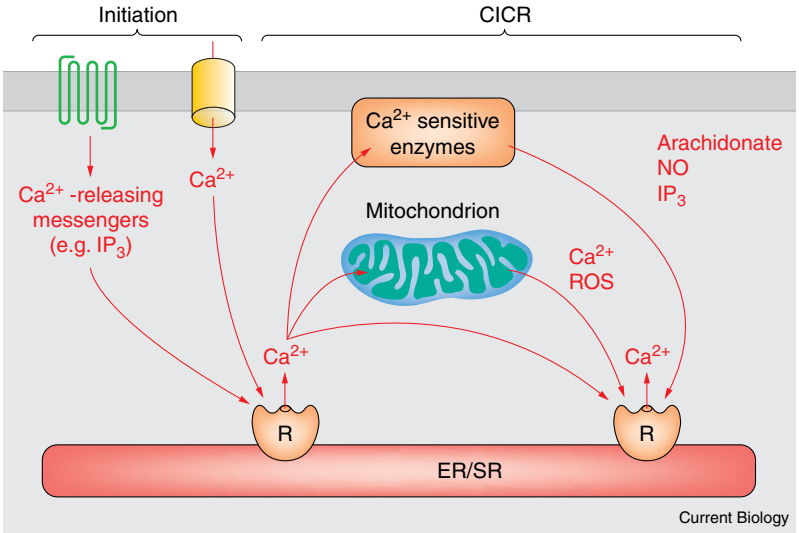

Figure 1.
This cartoon depicts how CICR mechanisms amplify calcium signals. Starting from the left-hand side, the figure illustrates the initiation of a calcium signal via an intracellular channel ('R''). This leads to direct release of calcium from neighbouring channels or production of calcium-releasing messengers.